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14. ABSTRACT.

In the last year we have combined results from Phase I and Phase II together, and added additional datasets from pre-existing trials to our prediction database. In Phase I we showed that an RNA-based gene signature from a sample taken at sea level could be used to successfully predict in 9 out of 10 individuals who went on to develop acute mountain sickness or who was AMS resistant. In Phase II, results suggest a completely independent sample was equally effective in predicting AMS susceptibility and resistance. We have added data from our AltitudeOmics study for a higher altitude with more severe AMS. Those results were also promising with over 90% of cases of severe AMS accurately predicted. Then in 2016 we waited for the possibility of getting and adding samples from a trial at US ARIEM. Now only at the end of 2016 did it become clear that funding for that new part of the project would not happen until maybe late in 2017. So the decision was made to finish the project by December 2017 with the data we have, and prepare to add other data later as part of a new project, if at all. All of the existing data are now being analyzed in one integrated test to assess effectiveness.

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INTRODUCTION:

The goal of this project is to design an easy-to-use cost-effective test that accurately predicts whether or not someone is likely to develop acute mountain sickness (AMS) when they travel to high altitudes.

OVERALL PROJECT SUMMARY:

Following program reviews over the last 24 months we have expanded the scope of the study and received a no cost extension to complete this expanded scope. To date in 2016 we have shown that all of the experiments can produce positive predicitons with reasonable sensitivity when tested independently. Now the challenge as we finish this project is to dig deep in a search for commen predictive signatures across all data sets, or at most two predictions, one for low to moderate altitudes and one for very high altitudes. Much of 2016 was spent waiting for funding options to be realized to add samples from a large study with US ARIEM. We knew this might happen which is why we asked for a two-year no cost extension through the end of 2017. So in spite of this waiting period we are about on track with our timeline ot finish our data analysis this coming fall. Those did not pan out. In addition, we are applying for additional funding through an independent DoD mechanism to cover some of the work we will do with US ARIEM on related projects.

QTR 17 Accomplishments (Jan-Mar 2016):
As planned we addressed specific questions about generalizability of the prediction algorithms across AMS severity, altitude of origin, altitude of final study, and gender.

We continued work for IRB compliance, and we worked on the HRPO DOD process to keep the AMS Prediction protocol open for research. That work is ongoing and will continue for remainder of the time we work on this grant.

We completed the request for a no cost extension. And we began the process of integrating some additional new data from US ARIEM into our workflow.

QTR 18 Accomplishments (Apr-Jun 2016):
As planned we continued to address specific questions about generalizability of the prediction algorithms across AMS severity, altitude of origin, altitude of final study, and gender.

We continue work for IRB compliance, and we have to work on the HRPO DOD process to keep the AMS Prediction protocol open for research. This work is ongoing and will continue for remainder of the time we work on this grant.

We also wrote a small DoD grant to fund the analysis of US ARIEM supplied samples. This was not funded, but other sources are being pursued to get this funding.

QTR 19 Accomplishments (Jul-Sep 2016):
Continued addressing specific questions about generalizability of the prediction algorithms across AMS severity, altitude of origin, altitude of final study, and gender.

We continue work for IRB compliance, and we have to work on the HRPO DOD process to keep the AMS Prediction protocol open for research. This work is ongoing and will continue for remainder of the time we work on this grant.

We made major progress on testing the intermediate samples from the AMS Prediction I study. By two independent techniques conducted by two independent bioinformatics analysts we determined that there is

substantial predictive power even in the largely 'grey' area of intermediate responses. That analysis will now be folded in to the overall analysis of all samples for the ultimate goal, and our last step on this project, identification of the most universal prediction methods.

QTR 20 Accomplishments (Sep-Dec 2016):

Anticipating a lack of US ARIEM funding and data we completed software construction of our database of all studies. This took considerable effort to make sure all studies have the same data coding for all variables in the database. We continue work for IRB compliance, and we have to work on the HRPO DOD process to keep the AMS Prediction protocol open for research. This work is ongoing and will continue for remainder of the time we work on this grant. Throughout all four quarters of 2016 we have had to commit considerable time and resources to continuing IRB review, both locally here in Colorado and at HRPO, which we have done and will continue to do. Even for a project that is not gathering new data, the IRB process takes a lot of time ech year.

KEY RESEARCH ACCOMPLISHMENTS:

- confirmation of our ability based on a sea level test in Phase I to predict acute mountain sickness at high altitude
- addition of data from our companion study, AltitudeOmics, to the database of gene studies to be analyzed for AMS prediction
- expansion of a bioinformatics team to include an additional consultant
- expansion of the bioinformatics dataset to include advanced clustering analysis which may lead to identification of biological factors linking the AMS prediction signature to biological mechanisms

REPORTABLE OUTCOMES:
Though the initial results are exciting, and verify our original hypothesis, it is premature to proclaim complete success. Today it is accepted practice to validate gene expression findings in an independent cohort before relying on the validity of a gene expression screening test. We are expanding this validation phase to include different samples from higher altitudes, and more samples from Phase I with less severe symptoms. In total now in our hands are data to analyze the prediction of AMS from samples collected from Denver residents studied in a chamber at 4500m, sea level residents studied at 5200m, sea level residents in two different protocols studied at 2800m. We waited for much of 2016 for the possibility to get US ARIEM samples, but that process is simply not moving along at appreciable speed. So we decided late in 2016 to go ahead and get the project done with the data in hand. This robust approach to validation will rigorously test whether AMS prediction from a sea level blood test is possible.

CONCLUSION:
The results are promising, the database of studies has been greatly expanded at no extra cost on this base contract, and in the next 6 months we should answer the question about the generalizability of the results of our previously successful tests--do they work at all altitudes in all combinations. This last step has potential to change the way we manage risk in people who have never before gone to high altitude.